

macrophagic nodules. The virus-laden gel was rapidly engulfed by the local phagocytes. Four days later the animals were sacrificed by air embolus, the vaccinated nodules removed, frozen in liquid nitrogen, ground to an impalpable powder, and extracted at ice-box temperature in ten volumes of physiologic sodium chlorid solution. The 10 per cent extracts thus obtained were centrifuged and filtered through a Seitz asbestos pad to remove any residual vaccinia virus. The filtrates were then titrated for virucidal properties.

Titration from nineteen rabbits showed that 0.05 cubic centimeters of the 10 per cent tissue extract almost invariably continued at least four virucidal units, each unit being defined as the amount necessary to neutralize one infectious skin dose of homologous vaccinia virus. This is equivalent to 1,000 extractable virucidal units per gram of macrophagic tissue. Control tests showed that in seven of the locally vaccinated rabbits no trace of virucidal action was demonstrable in the undiluted blood serum, nor in control extracts from the spleen, liver, or bone marrow. The conclusion seems warranted that the vaccinated skin nodules were the sites of formation of the virucidal antibodies. This is the first unequivocal evidence of specific antibody synthesis by local reticulo-endothelial tissues.

But many immunologists believe that it eventually may be shown that other tissue cells of the animal body are capable of specific immunologic adaptations. They recognize, however, that this belief is based on an earlier and now generally discarded preformist theory, and that macrophagic immunity is the only type of local tissue immunity thus far fully established by experimental evidence. Until this proof is available, direct vaccination of the brain and spinal cord will remain a pure biologic gamble.

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The rapid decline in tuberculosis mortality rates has been due mainly to lessening in the incidence of infection. Among those infected, the toll, though diminished, is still appalling. Mortality statistics, morbidity reports, autopsy examinations, tuberculin tests, and x-ray surveys indicate that about half of all infected individuals develop clinical tuberculosis, and that from 10 to 20 per cent of them eventually die of the disease. The high risk of disease and death due to infection by the tubercle bacillus justifies increased efforts for its prevention.—Emil Bogen, M. D., *American Review of Tuberculosis*, August, 1940.

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*Selection of Blood Bank Donors.*—Only those persons who have been born in this country and who have never lived in districts where malaria is prevalent should be used as donors for blood banks, Ernest F. Gordon, M. D., Yonkers, New York, advises in *The Journal of the American Medical Association*. He says that such a policy will minimize the possibility of spreading the disease from man to man. The first recorded case of an accidental transmission of malaria through transfused stored blood is reported by him.

## ORIGINAL ARTICLES

### SOME FACTORS INVOLVED IN THE CARE OF THE PATIENT SERIOUSLY ILL WITH BILIARY TRACT DISEASE\*

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THE intimate relationship of cholecystitis and hepatitis, generally accepted by most observers, must indicate that, in most instances, when a stone passes into the common bile duct there is apt to be an existing hepatitis before the effect of ductal occlusion still further damages the liver cells. That extensive hepatitis may coexist with simple gall-stone disease is not so generally accepted, but it is nevertheless true. The occlusion of the common bile duct by a stone is further complicated by the fact that, in most instances, the gall-bladder is at that time moderately or severely damaged. Under such circumstances the failure of the gall-bladder to concentrate the trapped bile leads to a rapid increase in the extra- and intrahepatic bile pressure, so that hepatic secretory suppression occurs at an earlier period after obstruction.

The opportune time, therefore, to operate on a patient with gall-stones is early, when the stones are still present in the gall-bladder and when the patient is suffering from the classical dyspepsia, or colic, or both, of simple calculus disease. It is, moreover, of importance to remove any calculi from the common duct at the primary operation. The time-honored concept that a previous history of jaundice is the indication for common-duct exploration has too frequently resulted in the primary or secondary operation being done following extensive liver injury, or even during a period of intense obstructive jaundice, when the risk of operation is greatly increased. Palpation of the common duct is a poor method of accurately determining the presence of stones, and the majority of stones found at a secondary operation are the result of faulty exploration of the extrahepatic bile passages at the primary operation. The surgeon can gain little relief from a troubled conscience lest the standpoint that the stones may have formed in the common duct subsequent to cholecystectomy.

#### FUNCTION TESTS

It is during a state of partial liver insufficiency that many of these seriously ill patients come for surgical aid. It is important, therefore, to determine, if possible, the exact degree of hepatic insufficiency which may exist. It is possible in those organs whose functions are few in number to make accurate functional tests, but this becomes exceedingly difficult in an organ whose activities are manifold, and in which the impairment of each function is not of the same degree.

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The glucose and galactose tolerance tests have been widely used, but we have often found them of little significant help. Alimentary glycosuria and alterations of the sugar tolerance curves are much too common in many pathological conditions to make these tests of serious diagnostic importance, especially in the milder or moderate types of hepatic derangement.

The glucose tolerance curves in some of the patients are not unlike those seen in diabetes. These high sugar tolerance curves are seen in patients whose fasting blood-sugar levels may be quite low, as we would expect in the presence of serious liver injury. It is generally believed that the glycogen storage of the liver is its major function, but it is much less generally recognized that the protein activities of the liver are of perhaps equal, or even greater importance.

Certain of the liver function tests have been based upon the ability of the normal liver to synthesize urea from ammonium carbonate. The tremendous reserve factor of the liver prevented the fulfillment of such prophecies, for 80 per cent of the liver of the dog can be removed without appreciably affecting normal urea formation. Even when amino-acids have been fed in large amounts, thus putting the liver under an increased strain, the results obtained in the presence of moderate liver damage have not been significant. The ability of the liver to synthesize urea is impaired only when the destruction of liver tissue is nearly complete, a time at which a function test is of little value.

The same, in large measure, is true of the tests based upon the conjugation of hippuric acid. While Quick's test is useful, it is not always infallible. The dye tests have also often proved disappointing. In the presence of incomplete ductal occlusion it is not at all infrequent to obtain a nearly normal disappearance curve of sodium tetraiodophenolphthalein from the blood. The determination of cholesterol fractions and other constituents in the blood are of help, but they too frequently may lead one astray.

The reserve capacity of the liver is so great that normal activity can be carried on by only a small part of the total liver mass, provided that is normal. And, finally, even though all the functions preoperatively are normal, the injury to the liver cells, as the result of operative trauma and anesthesia, may be so great as to convert a normally functioning liver into a completely incompetent one. We have found this to be true when the original liver glycogen concentration was twice the normal. It is necessary, therefore, at this time that we do not place too great reliance upon liver-function tests. Too frequently they give us a sense of security which is unwarranted.

For the determination of bile-pigment retention in the blood, we believe the Van den Bergh reaction is the most satisfactory method now available. Regardless of whether you agree on the specificity of the qualitative reaction, the quantitative portion of the examination remains the most accurate method available in the clinical laboratory for the determination of bilirubin concentration.

#### PREOPERATIVE CARE

In no field of surgery has the physiologic approach to the problems of pre- and postoperative care had a greater influence, or saved more lives than in the treatment of advanced biliary tract disease. The high mortality in the past can be ascribed neither to less technical skill nor to poorer surgical judgment, but rather to the lack of information concerning the pathologic physiology of the processes involved and the manner by which they can best be controlled prior and subsequent to operation. The special methods of preparation and after-care have been based in large part on experimental studies. It is now time that we evaluate the effects of special treatment on our clinical results.

The preoperative preparation of the patient should be directed toward correcting, so far as possible, any existing collateral disease, and improving the content of the hepatic cells so as to prevent further liver injury. I shall not discuss coexisting cardiac or pancreatic disease, except to state that neither of these conditions should be considered as insurmountable barriers to operation. If the patient is properly prepared, prior to operation, with the help of a competent internist, the added risk of either of these conditions is not great.

Angina pectoris may be mimicked in every way in gall-stone disease. We have had a number examples of this when stones have been present in the common duct, even though jaundice has never been present. Surely, operations on, or injections of the sympathetic nervous system should not be undertaken without first subjecting the patient to adequate surgery for the gall-stone disease.

It is generally believed that hepatic disease is unassociated with renal dysfunction. While as a rule this may be true, there occurs in a number of patients with obstructive jaundice a serious impairment of the functional activity of the renal parenchyma. It is in this group of patients that a low-serum calcium may be encountered, which is nearly always associated with a serum protein deficiency or with hyperphosphatemia. These are even more apt to be present if the patient had preëxisting renal disease. A preoperative high blood non-protein nitrogen, in these patients, is not always of serious significance, for subsequent to surgical therapy the evidences of renal injury may rapidly subside. In the absence of a history of previous renal injury the high blood nonprotein nitrogen concentration need not alarm one unnecessarily, unless the entire clinical picture, at the same time, warrants it.

The evidence of renal impairment should, in the main, be considered as an additional load which has been added to that which the patient is already carrying. It must be taken into account in preparing the patient for operation, and in determining the anesthetic to be used for operation. Above all, it must be considered in the administration of fluids, especially large amounts of sodium chlorid, which may so tax a renal system, when it is near the breaking point, as to result in renal insufficiency.

## DISTURBANCES IN LIVER PHYSIOLOGY

The advent of ductal occlusion causes serious disturbances in the physiology of the liver. The cells continue to secrete bile until the pressure in the bile ducts equals the secretory pressure of the liver. The presence of impaired gall-bladder function results in a shorter period of time between occlusion and icterus. When the intrahepatic bile pressure reaches from 280 to 330 millimeters of the bile, pigment does not pass through the cells and deep icterus results. Any further secretion is from the cells lining the ducts, and results in the formation of what is commonly called "white bile."

The increase in ductal pressure causes a retardation of the portal blood flow and thus there is set up a vicious circle for the development of an anoxemia in the hepatic tissue, in the face of evidence of an increased oxygen consumption in the liver during obstructive jaundice. Since the liver cells are extremely sensitive to oxygen want, further hepatic injury ensues. Thus, the primary hepatitis, if this was present, is accentuated by the increased pressure in the intrahepatic bile ducts, and by the secondary anoxia. The injured liver cell is less capable of holding and of storing glycogen. It rapidly loses its mobile protein, and since it is incapable of metabolizing the fat which comes to it there is apt to occur considerable fatty infiltration. The latter process is more apt to take place where there is considerable fat in the subcutaneous tissues.

While it was previously believed that the liver glycogen protected the liver against injury during anesthesia, information which we have collected leads us to state that it is the liver fat which conditions liver necrosis subsequent to the use of volatile anesthetics. The increase of the liver glycogen is valuable, therefore, only if, by increasing the liver glycogen, liver fat is reduced. Observations which we have made on a series of patients with common-duct occlusion, who were prepared by a high carbohydrate diet and the intravenous administration of glucose for from eight to fourteen days prior to operation, forces me to state that often there remained in the liver concentrations of fat which, had a volatile anesthetic been used, might have resulted in further serious liver injury.

## DIET AND INTRAVENOUS THERAPY

The plan which we are now using is as follows: The patients, if they can be made to eat, are given a diet which consists of 80 per cent of carbohydrate, to which is added protein in an amount of 20 per cent of the total calories. The diet is given in small amounts, but at frequent intervals, so that the total caloric intake is about 3,000 calories per day. The protein is added because it is the best substance for man, available at this time, to assist the carbohydrate in displacing the liver fat, and, furthermore, tissue regeneration cannot take place without sufficient stores of protein. In addition to the carbohydrate-protein meal, we give these patients approximately 10 milligrams of crystalline vitamin B<sub>1</sub> daily. The latter improves the appetite. The addition of protein and B<sub>1</sub> to our previous routine

has, we believe, resulted in a marked reduction in the liver fat and resulted in a distinct improvement in the condition of the liver cells. With such a method we have increased the liver glycogen concentration in the presence of complete ductal occlusion in the experimental animal to as much as 12 per cent, a concentration which we previously had thought unattainable, and a simultaneous reduction of the liver fat from levels as high as 50 per cent to a normal level over a period of two weeks.

## VITAMIN K AND BILE-SALT THERAPY

The use of substrates containing vitamin K<sub>1</sub> or K<sub>2</sub>, or of the synthetic quinone derivatives having a K-like action, has made postoperative hemorrhage an exceedingly rare complication. Two methyl 1—4 naphtha quinone, in doses of two milligrams three times a day, is effectual in restoring a normal prothrombin time in the great majority of patients within seventy-two hours. It is even more potent than the naturally occurring vitamin.

The hemorrhagic tendency of the jaundiced patient is due to a prothrombin deficiency conditioned by the absence of bile salt from the intestinal tract. When the vitamin K substrates are used, bile salts must be used with them.

## TIME FOR OPERATION

We have come to believe that early operation, once occlusion has occurred, is not always to be desired. The suggestion of Waltman Walters that the obstructed patient be operated on at a time when the level of the bilirubinemia is stationary, is an excellent one. It has been our policy to withhold operation when the bilirubin concentration in the serum is increasing or decreasing. If it is increasing or decreasing, we wait until the concentration reaches a plateau. During this period the patient is being prepared for operation. The operation is safer when hepatic function has stabilized itself against a high or low-serum bile pigment concentration.

All severely jaundiced patients who have not responded to K therapy are placed on a diet for from ten to fourteen days and are transfused prior to operation. Our practice has been to use small amounts, 250 to 300 cubic centimeters of blood for two or three days before the contemplated exploration. This serves several purposes. It improves the quantity and the quality of the blood; it provides serum protein, which may be deficient, and it improves the oxygen-carrying capacity of the blood.

## ANESTHESIA

In the light of available evidence at this time, we believe that the anesthetic of choice is spinal anesthesia. We have good evidence that ether may cause serious liver injury in the presence of the conditions often existing during ductal occlusion. Nitrous-oxid and oxygen, when pushed to the point of even semi-satisfactory relaxation, causes anoxia which results in further liver injury. Cyclopropane may be satisfactory, but there is as yet insufficient evidence as to its effect on the hepatic parenchyma to warrant its widespread adoption.

Spinal anesthesia, in which marked depression of the blood pressure is prevented by the preanesthetic administration of adequate doses of ephedrin, has proved so satisfactory in our hands that until a better method is demonstrated we shall continue to use it. Carefully administered, it is, we believe, the safest anesthetic in these bad-risk patients.

#### INCISION

We believe that the subcostal incision affords better exposure of the biliary passages, is associated with less postoperative pain, fewer pulmonary complications, and a lower incidence of postoperative herniation than any other incision. Its full advantages are never appreciated until it is used.

I shall not discuss the various technical details necessary satisfactorily to complete the operation. In the presence of stone obstruction a thorough search is essential and the removal of a single stone is not sufficient reason for terminating the exploration. Not until the operator is satisfied that there are no stones in the right or left duct, and a catheter can be freely passed into the duodenum, is his responsibility for further exploration at an end.

#### POSTOPERATIVE CARE

As soon as the opening in the common duct is closed around the tube, fluid is introduced through the open end of the tube and the tube is then clamped. When the patient is returned to his bed the free end of the tube is attached to a decompression apparatus, so arranged that the top level is kept at approximately 200 millimeters above the common duct. Over a period of days this is gradually lowered, but it is never lowered to the point where large amounts of bile are permitted to drain externally.

The use of this principle serves several useful purposes. In the first place, it prevents an acute hepatic hyperemia subsequent to release of the ductal occlusion. After the sudden release of a complete ductal occlusion, there is often observed an intense hyperemia of the liver tissue and the extravasation of large amounts of blood in the perivascular spaces. Although decompression occurs in part during the operation, the maintenance of an adequate pressure level thereafter is, we believe, of real help in preventing massive extravasation of blood into the liver tissue. Furthermore, it overcomes the defect of the older method of drainage into a bottle at the bedside in that large amounts of bile are not sucked into the container. The added advantage of permitting the bile to enter the intestine at an early period is obvious. The fluid and electrolyte balance is more easily maintained and the extrahepatic functions of the bile are reestablished within a short time after operation. The effects of excessive external bile drainage were described some years ago by William Halsted, who personally experienced them. The lassitude, weakness, anorexia, rapid pulse, and even comatose state, so frequently observed in such patients, can in large measure be prevented by the use of the decompression principle. The additional advantage of the bile subserving a useful intestinal function, I shall describe at a later period.

#### CHOLANGIOGRAMS

No tube should be removed from the common duct before doing a cholangiogram. Even the most experienced of surgeons will occasionally leave a stone behind. The time to know this is before the "T" tube is removed.

#### POSTOPERATIVE FLUIDS AND DIET

In the administration of fluids during this period, one must be guided by the principles laid down by Wiley and Newburgh and their elaboration by Collier and Maddock. The control of the postoperative administration of intravenous fluids to these patients is not to be left to one of a group of constantly changing internes, nor can the quantity or type be determined routinely for all patients.

As soon as the stomach is retentive, food should be given by mouth. The diet which we have used in the postoperative period is again a carbohydrate-protein mixture, practically devoid of fat. With such a régime, regeneration of liver cells may occur rapidly, and normal function, if this can be restored, will make its appearance at an earlier period than when the patient is on a haphazard diet or a program which restricts food by mouth beyond the necessary period. It is not possible to furnish the energy requirements of the patient and increase the liver glycogen and protein storage by intravenous therapy. Protein wastage will be prevented, liver glycogen stores will be built up, liver fat displaced, and cell regeneration takes place when the total food intake is sufficient to more than cover the energy requirements.

#### BILE THERAPY

The restoration of bile to the intestinal tract at an early period by the use of a decompression apparatus, if the lower end of the common duct is patent, has already been mentioned. The most important function of the bile is its intestinal function. The activation of lipases, the emulsification of fats and their transport across the intestinal membrane, and the aid in the absorption of accessory food substances, are but a few of the activities which bile plays in the small bowel.

For some time we replaced part of the bile drained to the exterior through a gastric tube, and still use this method when edema or inflammatory exudate prevent the entrance of bile directly into the duodenum. For the past six years we have kept a store of fairly normal bile drained from patients and have had this lyophilized by the method of Flosdorf and Mudd. This dehydrated human bile is thus available for use by adding distilled water and provides a useful source for such material. It is useful also when a cholecystostomy has been done as a primary procedure for obstructive jaundice in inoperable malignancy of the pancreas, to be followed when the icterus has disappeared by a secondary short-circuiting operation.

With the decompression method, bile flows directly into the duodenum. Convalescence is smoother, and we have had an absence of the asthenic states which were so often observed where excessive external biliary drainage occurred. The asthenia (which Doctor Whipple, for want of a

better name, called "pancreatic asthenia") has not been observed by us since we began the routine use of decompression eight years ago. It is, we believe, due to a disturbance of intestinal and hepatic physiology and is the result, in part, of an interference with the extrahepatic functions of the bile. Why it makes its appearance in some patients and not in others; and why it is often not observed after prolonged ductal occlusion prior to operation, I cannot explain.

I have discussed a few of the factors which we must consider in caring for these desperately ill patients before, during, and after operation. In each of them there are present certain profound physiological disturbances, some of which are understood and others of which remain to be elucidated. The risk of operation will be reduced if attempts are made prior, during, and subsequent to operation to restore function to as nearly normal as may be possible. Such a program has resulted in a very desirable reduction in the morbidity and mortality of operations for the seriously ill patient. Further improvement in our immediate and late results will come from a fuller understanding of the conditions imposed on the organism during icterus of the obstructive type; for, regardless of the skill of the operator, mortality will remain higher than it need be if the pathologic physiology is disregarded.

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### AN ANALYSIS OF CAUSES OF DEATH IN PROSTATECTOMY\*

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THE problem of mortality reduction from prostatic surgery is not a simple one. The selection of the most favorable time for operation, the question of the most suitable procedure, and the need to combat postoperative complications are a constant challenge to the judgment, skill and, not the least of all, the alertness of the surgeon. Many of these factors are of such variability that it is next to impossible to draw therefrom dependable conclusions. However, in a consideration of the "cause of death" we are frequently able, by summing up the entire case, to discover where errors of technique or judgment entered and thus, by recognizing the pitfalls, avoid them in the future. It was with this hope that the following paper was written.

#### CLINICAL MATERIAL FOR THE STUDY

The material for this study was drawn from the clinical records of eighty-seven patients who died following one of the three accepted operations for the relief of bladder-neck obstruction. The records are from approved hospitals in the San Francisco Bay region and from the services of qualified urologic surgeons. In this series the total mortality was 14.16, classified as follows: suprapubic, 12.8; transurethral resection, 11.7; perineal, 7.3.

\* Chairman's address, read before the Section on Urology of the California Medical Association at the sixty-ninth annual session, Coronado, May 6-9, 1940.

The high death rate was due, in part, to the fact that many of the patients were, in many instances, of the county hospital type. It is perhaps fair to point out that the high percentage noted in transurethral resection was in a large measure influenced by two factors: first, the universally admitted high mortality seen in the early days of this operation (in the years 1932 and 1933) due to inexperience and inadequate equipment; and, second, the habit of utilizing transurethral resection in poor risks, where previously such cases would have been considered inoperable. An improvement is seen in the year 1938, when the mortality from four services (including the County Hospital) was 1.3 per cent.

Seventy of these patients were operated upon under spinal anesthesia, four under spinal anesthesia reinforced with NO<sub>2</sub> and ether, five under NO<sub>2</sub> and ether, four under NO<sub>2</sub> and O, two under pentothal sodium intravenously, and one under paraldehyde per rectum. Those who were not operated upon under spinal anesthesia do not appear to have had any special indication for the anesthetic selected, and were probably victims of a transient investigative impulse on the part of the surgeon.

#### CAUSES OF DEATH

In considering the causes of death, those related to cardiac disease, cerebral accident, hemorrhage, and sepsis have been of special interest.†

#### CARDIAC DEATHS

Thirty patients died of cardiac disease, coronary disease or cerebral accident. Of this number, 70 per cent of those dying of cardiac disease, 55 per cent of those dying of coronary occlusion, and 60 per cent of cerebral accident gave past histories of auricular fibrillation, previous cerebral accident, edema of ankles, dyspnea, or showed an unfavorable prognosis after an electrocardiogram. While, of course, there are many prostatics who, with similar past histories, have successfully withstood prostatic surgery, emphasis must be laid upon the value of a searching inquiry into the past history, and an appreciation of the ominous influence of a bad history, upon the prognosis.

The group of patients dying of cardiovascular disease did not, as a whole, show more than the usual degree of arteriosclerosis or hypertension associated with the aged. The average blood-pressure readings were for those dying of cardiac failure, 141/83; of coronary disease, 153/70; and of cerebral accident, 173/95. These pressures are the averages resulting from several observations and they are probably true readings.

Of the twenty-four patients dying of cardiac disease, nine died of coronary sclerosis. An effort was made to connect the sudden drop of blood

† Slide showing deaths in cardiac, cerebral hemorrhage, sepsis, hemorrhage and miscellaneous.

	Per Cent	Number	Perineal	Suprapubic	Transurethral Resection
Cardiac .....	27.5	24	4	10	10
Cerebral accident .....	8.7	6	0	1	5
Hemorrhage .....	24	21	0	7	14
Sepsis .....	28	25	6	11	8
Miscellaneous .....	12.5	11	0	9	2